Microwave-Assisted Silyloxy-Cope Rearrangement of *syn*-Aldol Products in DMF: Enhancement of Rate and Diastereoselectivity

Christoph Schneider,* Souad Khaliel

Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: schneider@chemie.uni-leipzig.de

Received 16 February 2006

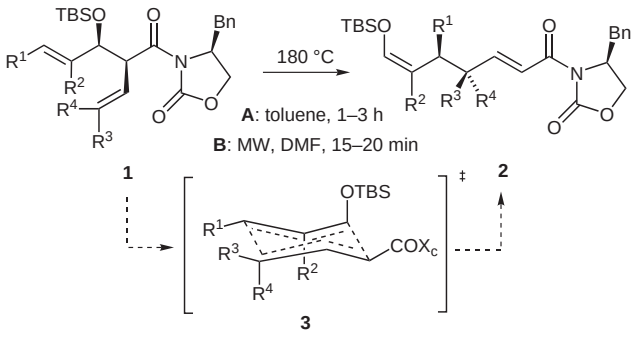
Abstract: Microwave-assisted Cope rearrangements of 1,5-dienes embedded in a *syn*-aldol structure proceed in substantially reduced reaction times and markedly increased diastereoselectivity when conducted in DMF as solvent.

Key words: aldol products, Cope rearrangement, diastereoselectivity, microwave irradiation

[3.3]Sigmatropic rearrangements belong to the most fundamental organic transformations and improved variants continue to broaden the scope of this reaction family. Their predictable stereospecific reaction path through a chair-like transition state and a documented complete chirality transfer offers the possibility to provide products of high stereochemical purity which are otherwise not easily accessible.[1]

In this context we have developed the silyloxy-Cope rearrangement of 1,5-dienes **1** embedded in a *syn*-aldol structure[2] which are directly available using the Evans asymmetric aldol methodology.[3] A rapid, high-yielding, and stereoselective Cope rearrangement occurs when 1,5-dienes **1** are heated in toluene at 180 °C (sealed flask) for 1–3 hours depending on the degree of substitution (Scheme 1). Whereas 1-monosubstituted 1,5-dienes (R^1 = alkyl, R^3 and R^4 = H) typically rearrange within 1 hour at 180 °C, 1,6-disubstituted 1,5-dienes require extended heating for 2–3 hours at 180 °C for complete conversions. In analogy to the classical Doering experiments[4] we have proposed the chairlike transition state **3** to account for the observed diastereoselectivity of the rearrangement giving rise to the Cope products **2** with a *Z*-configured silyl enol ether and an *E*-configured enimide double bond. The minor diastereomers (not shown here) originate from the inverted chair-like transition state furnishing products with opposite stereochemistry at every stereogenic element. The Cope products **2** have proven to be valuable synthetic intermediates in the synthesis of enantiomerically pure cyclohexanes, tetrahydropyrans, piperidines, polyols, and terpenes.[5]

We have now found that the reaction times for the [3.3]sigmatropic process can be significantly reduced when the rearrangement is performed under microwave conditions.[6] At the same time the diastereoselectivity of this process is markedly improved using DMF as solvent. The selection of DMF as solvent was made on the consideration that only solvents with a sufficiently high dielectric constant are capable of absorbing the electromagnetic radiation efficiently and converting it into heat.[7]



Scheme 1 Cope rearrangement of aldol products **1** under standard (A) and microwave (B) conditions.

When 1,5-diene **1a** was irradiated in a microwave reactor at 180 °C in DMF as solvent for just 15 minutes, the Cope product **2a** was formed in 91% yield and 25:1 diastereoselectivity (Table 1, entry 1).[8] This compares favorably with our standard thermal reaction conducted in toluene which requires a reaction time of 1 hour and gives rise to a 10:1 diastereoselectivity. The temperature in the microwave oven could even be lowered to 140 °C and still **2a** was formed within just 30 minutes in 90% yield. Other 1-monosubstituted 1,5-dienes **1b**–**d** rearranged under identical microwave conditions in high yields and excellent diastereoselectivities of >25:1 for all examples were tested (entries 2–4). Whereas 1,5-dienes **1b** and **1c** displayed comparable, albeit reduced selectivities in the thermal reaction in toluene, the selectivity for the silyl-substituted 1,5-diene **1d** was markedly increased from 5:1 to >25:1 (entry 4).

The same trend was observed for more highly substituted 1,5-dienes carrying alkyl groups both in the 1- and 6-position. Thus, **1e**–**g** rearranged in good yields and very high diastereocontrol (>25:1) within only 20 minutes to furnish Cope products **2e**–**g**, respectively, with two new chiral centers (Table 1, entries 5–7). On the contrary, the thermal reactions of **1e**–**g** in toluene at 180 °C required 2–3 hours for complete conversions. In all cases the stereochemical outcome of the rearrangements was consistent with the chair-like transition state **3** depicted in Scheme 1.

SYNLETT 2006, No. 9, pp 1413–1415
Advanced online publication: 22.05.2006
DOI: 10.1055/s-2006-939729; Art ID: G06306ST

Table 1 Cope Rearrangements of Aldol Products **1** under Microwave (DMF, 15–20 min) and Standard (Toluene, 1–3 h) Conditions at 180 °C

						Microwave conditions		Standard conditions	
Entry	1,5-Diene	R^1	R^2	R^3	R^4	Ratio[a]	Yield (%)[b]	Ratio[a]	Yield (%)[b]
1	**1a**	Me	H	H	H	25:1	91	10:1	87
2	**1b**	Me	Me	H	H	>25:1	87	>25:1	82
3	**1c**	Ph	H	H	H	>25:1	79	20:1	80
4	**1d**	$SiMe_2Ph$	H	H	H	>25:1	85	5:1	85
5	**1e**	Me	H	Me	H	>25:1	90	>25:1	87
6	**1f**	Me	H	Et	H	>25:1	79	>25:1	75
7	**1g**	Me	Me	Et	H	>25:1	81	>25:1	70

[a] Determined by ^{1}H NMR and ^{13}C NMR of crude product.
[b] Isolated yield of purified material.

Kinetic experiments indicate that the reaction rate was independent of the solvent used. Thus, **1a** was rearranged with a half-life of $t_{1/2}$ = 12 min in toluene as well as in DMF at 180 °C under standard conditions. The half-life decreased, however, to $t_{1/2}$ = 3–4 min under microwave conditions with DMF as solvent at 180 °C. This rate-accelerating effect is believed to originate from a more efficient conversion of electromagnetic radiation into heat and hence a more rapid heating of the reaction mixture than under normal conditions.[7]

The origin of the significant enhancement of diastereoselectivity in DMF as solvent, which was also observed under usual thermal conditions, is not entirely clear at the moment. We have previously noted that the *syn*-aldol structure of 1,5-dienes **1** with an electron-rich allyl silyl ether fragment and an electron-poor allyl carboximide fragment is responsible for the high rate and selectivity of the Cope rearrangement.[2c] We assume that a highly polarized, yet still concerted, transition state may be involved in the rearrangement which is expected to benefit from the dipolar solvent. Theoretical calculations are currently ongoing to shed light on these mechanistic questions.

In conclusion, we have established a modified protocol for the execution of the silyloxy-Cope rearrangement of 1,5-dienes embedded in a *syn*-aldol structure with significant effects on the rate and diastereoselectivity. It takes advantage of the rate enhancement under microwave conditions and uses the highly dipolar solvent DMF to further enhance the diastereoselectivity of the process.

Acknowledgment

This work was supported by the Fonds der Chemischen Industrie. We thank Degussa AG for the supply of enantiomerically pure amino acids and Wacker AG for the generous donation of *tert*-butyldimethylsilyl chloride. Souad Khaliel is grateful to the University of Garyounis (Bengazi, Libya) for a doctoral fellowship.

References and Notes

(1) Reviews: (a) Nubbemeyer, U. *Synthesis* **2003**, 961; and references cited therein. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (c) Frauenrath, H. *Stereoselective Synthesis*, In *Houben-Weyl (Methods in Organic Chemistry)*, Vol. E21d; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, **1995**, 3301.

(2) (a) Schneider, C.; Rehfeuter, M. *Synlett* **1996**, 212. (b) Schneider, C.; Rehfeuter, M. *Tetrahedron* **1997**, *53*, 133. (c) Schneider, C. *Synlett* **2001**, 1079. For related work see: (d) Black, W. C.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37*, 4471. (e) Tomooka, K.; Nagasawa, A.; Wei, Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 8899.

(3) (a) Evans, D. A.; Bartroli, J.; Shi, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2128. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4957.

(4) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

(5) For the application of the Cope products in organic synthesis see: (a) Schneider, C. *Synlett* **1997**, 815. (b) Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73. (c) Schneider, C.; Börner, C. *Synlett* **1998**, 652. (d) Schneider, C.; Börner, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1999**, 3353. (e) Schneider, C. *Eur. J. Org. Chem.* **1998**, 1661. (f) Schneider, C.; Rehfeuter, M. *Tetrahedron Lett.* **1998**, *39*, 9. (g) Schneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850. (h) Schneider, C.; Reese, O. *Angew. Chem. Int. Ed.* **2000**, *39*, 2948; *Angew. Chem.* **2000**, *112*, 3074. (i) Schneider, C.; Reese, O. *Chem. Eur. J.* **2002**, *8*, 2585. (j) Schneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* **2002**, 2098.

(6) Davies et al. reported the microwave-assisted Cope rearrangement of a similar, but ester-derived aldol product in hexane (190 °C, 70 min) and an ionic liquid (240 °C, 45 min). Our results with the imide-based aldol products **1** compare favorably with these conditions. See: Davies, H. M. L.; Beckwith, R. E. J. *J. Org. Chem.* **2004**, *69*, 9241.

(7) Excellent review: Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; *Angew. Chem.* **2004**, *116*, 6408.

(8) **Typical Experimental Procedure.**
A microwave reactor 'microPREP A' (MLS GmbH, Germany) with a single magnetron (max. 1200 W, pulsed irradiation, 2.45 GHz) terminal 320 controller, and easy CONTROL 06 software was used for the microwave experiments. A power of max. 500 W was used in all

experiments and the temperature inside the reaction mixture was controlled with a ATC-FO 300 fiberoptic sensor inserted into the reaction vessel and automatically adjusted to the set temperature. The amount of 300 mg (0.70 mmol) of 1,5-diene **1a** was dissolved in 25 mL dry DMF and placed in a microwave vessel, which was sealed. The sample was irradiated for 15 min at 180 °C whereupon the solvent was evaporated in vacuo. The crude product was analyzed by NMR to determine the diastereoselectivity (25:1) and subsequently purified by flash chromatography over silica gel with Et_2O and pentane (1:6) to furnish 275 mg of the Cope product **2a** (91%) as a colorless solid. Mp 60–61 °C; $[\alpha]_D^{20}$ 13.0 (*c* 1.2, $CHCl_3$). IR (film): ν = 3027, 2956, 2858, 1782, 1681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 6 H, TBS), 0.92 (s, 9 H, TBS), 1.02 (d, *J* = 7.0 Hz, 3 H, Me), 2.28–2.32 (m, 2 H), 2.79 (dd, *J* = 13.0, 9.8 Hz, 1 H, benzyl-H), 2.90 (m, 1 H), 3.34 (dd, *J* = 13.0, 3.0 Hz, 1 H, benzyl-H), 4.14–4.23 (m, 2 H), 4.31 (dd, *J* = 10.0, 8.7 Hz, 1 H, 6′-H), 4.72 (m, 1 H), 6.16 (dd, *J* = 6.0, 1.0 Hz, 1 H, 7′-H), 7.21–7.36 (m, 7 H, 2′-H, 3′H, phenyl-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.30, –5.22, 18.35, 20.94, 25.76, 28.46, 38.06, 40.63, 55.45, 66.18, 115.10, 121.20, 127.40, 129.10, 129.60, 135.60, 138.30, 151.10, 153.50, 165.10. MS (EI, 70eV): *m/z* = 429 (1), 414 (10), 372 (20), 185 (100), 91 (45), 73 (99). Anal. Calcd: C, 67.10; H, 8.21; N, 3.26. Found: C, 67.14; H, 8.39; N, 3.13.